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**From:** Borin, Michael  
**Sent:** Tuesday, February 22, 2000 4:08 PM  
**To:** STIC-Biotech/ChemLib  
**Subject:** FW: Search request:08-619708;

Examiner: M Borin

AU: 1631; CM1 9-15

Tel.: 305-4507

RE: 09/132799. ~~KLVEF~~ peptides.

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Point of Contact:  
Emergency Encars  
Technical Info: Specialist  
CM1 12C14 Tel: 306-46394

Please conduct search + interference search of SEQ ID Nos. 1-3. Limit the results to >90% match

Thank you

11 ANSWER 1 OF 3 USPATFULL  
AN 96:34323 USPATFULL  
TI Octahydroindolizinepropanoic acids and related compounds as enzyme inhibitors  
IN Myndrise, Jon S., Indianapolis, IN, United States  
Eskoda, David S., Brownsburg, IN, United States  
EA Eli Lilly Company, Indianapolis, IN, United States U.S. Application No.  
FI US 4894431 19960601  
AI US 19-3-41946 19930301 1 2  
IT Utility  
EXNAM Primary Examiner: Brust, Joseph Paul  
LREP Scanlon, William B.; Whale, Arthur R.  
CLMN Number of Claims: 4  
ECL Exemplary Claim: 1  
IFWN No Drawings  
LN.CNT 991  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
FI US 4894431 19960601  
AB Octahydro-5-oxoindolizine-6-propanoic acids and octahydro-6-oxopyrido[1,2-A]pyridine-7-propanoic acids, the decarboxy and related ester and perhydro derivatives thereof inhibit angiotensin I converting enzyme and are hypotensive agents. Hydrogenation of A58365 factors A and B, obtained by culturing Streptomyces chromofuscus, provides the **ACE inhibitors**. Also provided are O-aryl and 3-sulfonyl derivatives of A and B factors which are useful in preparing deoxy factors A and B via hydrogenolysis.  
SUMM The **ACE inhibitors** known as A58365 factor A and A58365 factor B represented by the following structural formulae \*\*STR1\*\* produced by culturing Streptomyces chromofuscus NRRL 15199 are hydrogenated to the corresponding perhydro derivatives, 3-carboxyoctahydro-5-oxo-6-indolizinepropanoic acids and 4-carboxyoctahydro-6-oxo-7-pyrido[1,2-a]pyridinepropanoic acids, and the deoxy and decarboxy hydrogenolysis products, and the perhydro products of the latter. The hydrogenation and hydrogenolysis products obtained are useful hypotensive agents, in particular deoxy factor A obtained by hydrogenolysis of factor A. Certain acyl and sulfonyl derivatives of A58365 factors A and B are also provided as intermediates to deoxy factor A and deoxy factor B.  
SUMM The ACE inhibitory activity also can be demonstrated by the lowering of the **blood pressure** in sodium depleted rats treated with test compounds.  
SUMM The ACE inhibitory compounds of the invention as described hereinabove are useful for lowering the **blood pressure** in hypertensive mammals. The compounds or the pharmaceutically acceptable non-toxic salts thereof are administered to a hypertensive host in a **blood pressure** lowering dose of between about 1 mg and about 1,000 mg. For parenteral administration the compounds or the salt or biologically cleavable ester is dissolved or suspended in a

physiologically acceptable fluid for injection, either intramuscularly or intravenously. Suitable fluids or diluents such as Water-For-Injection, 0.9% saline, 5% glucose or other fluid may be used. For oral administration the compound or a salt or ester thereof may be formulated in gelatin capsules, tablets or liquid suspensions. The administration can be carried out with a single daily dose or multiple daily doses.

SUM24 Preferred **ACE inhibitors** are represented by the formula 1 wherein R and R.sub.1 are hydrogen, n is 1 or 2 and Y is  $\text{-dbd.CH--CH.dbd.-}$ .

SUM25 The compounds of the formula 4 are useful intermediates for preparing the **ACE inhibitors** deoxy factor A and deoxy factor B represented by the formulae 1c and 1f. In addition to their use as intermediates, the compounds represented by the formula 4 wherein R.sub.4 is a C.sub.2 -C.sub.5 alkanoyloxy group and the pharmaceutically acceptable salts thereof are also active **ACE inhibitors**. In particular, a preferred acyl derivative is the O-acetyl factor A which has demonstrated ACE inhibition activity in the same tests in which factor A and the reduction products of factors A and B of formula 1 demonstrated activity. Accordingly, the O-acyl derivatives of the formula 4 and the pharmaceutically acceptable, non-toxic salts and biologically active esters thereof are useful hypotensive agents in the treatment of hypertension.

SUM26 The A58365 factors A and B (formula 3) which are used as starting materials for preparing the **ACE inhibitors** of this invention are obtained by culturing a new strain of Streptomyces chromofuscus NRRL 15098 as described in co-pending applications serial Nos. 409,765 now U.S. Pat. No. 4,404,281 and 409,764 now U.S. Pat. No. 4,404,282, filed Aug. 19, 1982. The compound of the formula 3 wherein n is 1 is designated in the co-pending application as A58365 factor A, while the compound of the formula 3 wherein n is 2 is designated as A58365 factor B. As described in the co-pending applications, the compounds of the formula 3 are prepared by culturing Streptomyces chromofuscus NRRL 15098 under aerobic fermentation conditions in an aqueous nutrient culture medium containing assimilable sources of carbon, inorganic salts and nitrogen. The culture medium employed in the fermentation can be any one of a number of media since the microorganism is capable of utilizing energy from a variety of nutrient sources. For example, a variety of carbohydrates including sugars and starches can be included in the culture medium to supply the carbon requirements of the microorganism. Likewise, various sources of nitrogen such as the amino acids, distillers extracts, meat peptones, and casein hydrolysates can be employed in the culture medium. In the interest of economy in production, optimal yield, and ease of isolation of the ACE factors, certain culture media are preferred. For example, one of the preferred sources of carbon is potato dextrin, although various sugars such as glucose or fructose may also be used. Preferred sources of nitrogen are

02 22 1957

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peptones and the hydrolysates of casein. As is common in the fermentation of microorganisms, nutrient inorganic salts can be incorporated in the culture medium for the production of the ACE factors. Such inorganic salts are the customary salts capable of yielding sodium, potassium, ammonium, calcium, phosphate, chlorine, carbonate, and like ions. Trace elements may also be added to the fermentation medium; however, these are commonly added in sufficient trace amounts as constituents of other ingredients added to the media.

NOTE The microorganism employed in the method for producing the **ACE inhibitors** of this invention has been identified as a new strain of *Streptomyces chromofuscus* (Preobrazhenskaya, Blinov and Ryabova 1957), Pridham, Hesse and Benedict, "A Guide for the Classification of Streptomyces According to Selected Groups", Appl. Microbiol. 6:52-59, (1957).

12 22 1984

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Page 2

11 ANSWER 1 OF 3 USPTFULL

12 96128431 USPTFULL

13 Method of treating heart failure and medicaments therefor

14 Steffen, Robert P., Saline, MI, United States

15 Evans, Dale B., Saline, MI, United States

16 Kaplan, Harvey R., Ann Arbor, MI, United States

17 Weisbach, Jerry A., Ann Arbor, MI, United States

18 Warner-Lambert Company, Morris Plains, NJ, United States U.S.  
Corporation

19 US 4584299 19860422

20 US 1984-612275 19840521 46

21 Utility

EXAMINER Primary Examiner: Robinson, Douglas W.

1REP Thierstein, Joan

CLMN Number of Claims: 7

ECN Exemplary Claims: 1

DPWN No Drawings

INVENT 546

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 4584299 19860422

AB Method for treating heart failure by increasing myocardial contractility and cardiac output with the administration of a pharmaceutical composition containing a combination of active ingredients including a pyridazinone or pyridin-one cardiotonic agent and a tetrahydroisoquinoline-3-carboxylic or octahydro-1H-indole-2-carboxylic acid **ACE inhibitor**.

SUM1 Antihypertensive agents which attribute their activity to inhibition of angiotensin-converting enzyme (**ACE inhibitors**) have been described. For example, aryl derivatives of 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acids are described in U.S. Pat. No. 4,344,949 and acylated octahydro-1H-indole-2-carboxylic acids are described in U.S. Pat. No. 4,425,355.

SUM2 Combinations of antihypertensive agents and diuretics are well-known in the art. ACE-inhibiting antihypertensive agents have also been reported to be useful in combination with diuretic compounds in U.S. Pat. No. 4,217,347. Combinations of **ACE inhibitors** with diuretics, saluretics, alpha.-adrenolytics, beta.-blockers, calcium antagonists or vascular dopaminergic receptor agonists are reported in European Patent Publications 51,628, 69,946, and 49,658.

SUM3 The present invention relates to a combination of certain **ACE-inhibitors** with certain cardiotonic agents resulting in a synergistic increase in myocardial contractility and cardiac output thereby rendering such combinations useful in treating heart failure.

SUM4 The compounds of formulae I and II have been reported as cardiotonic agents and their effectiveness demonstrated in standard pharmacological test procedures, for example, in causing a significant increase in the myocardial contractility in the pentobarbital anesthetized dog with low

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or minimal changes in heart rate and **blood pressure**, see U.S. Pat. No. 4,353,905 and U.S. application Ser. No. 515,790 of July 22, 1963.

- SUM21 This invention relates to the discovery that the combination of a cardiotonic agent as defined above with an **ACE inhibitor** as defined above results in a synergistic increase in myocardial contractility and cardiac output and therefore may be used in pharmaceutical compositions for treating heart failure.
- SUM22 The **ACE inhibitor** components in the combination have asymmetric carbon atoms. The compounds accordingly exist as optical isomers and diastereomers or as racemates and mixtures thereof. All of these are within the scope of the invention. The 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid used in this invention has the L configuration. This configuration has been shown to be required for biological activity, and thus **ACE inhibitors** of the invention are derived from either L(-) or DL-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- SUM23 The antihypertensive **ACE inhibitors** can be produced as described in U.S. Pat. No. 4,344,949 for the isoquinoline-3-carboxylic acids and in U.S. Pat. No. 4,425,355 for the octahydro-indole-2-carboxylic acids. According to this invention, a combination of a cardiotonic compound and an **ACE inhibitor** is administered in an effective amount which comprises a total daily dosage of about 1 to 200 mg, preferably 1 to 20 mg of cardiotonic agent and about 1 to 100 mg, preferably 1 to 20 mg of the **ACE inhibitor** to a subject, e.g., a mammalian species, suffering from heart failure. Such total daily dosages can be used in a single administration of the total amount or in divided doses two to four times daily. Generally, once or twice daily is preferred. This preferred dosage is about 3 to 60 mg of cardiotonic agent and about 3 to 60 mg of the **ACE inhibitor** once daily or about 1 to 20 mg of cardiotonic and about 1 to 20 mg of **ACE inhibitor** twice daily. The preferred route of administration is oral.
- SUM24 The pharmaceutical compositions of the invention can take any of a wide variety of oral and parenteral dosage forms. The dosage forms comprise as the active components, a cardiotonic compound as defined previously and an **ACE inhibitor** as defined previously as free bases and free acids thereof or as corresponding pharmaceutically acceptable salts.
- TEST1 Barbiturate anesthetized, vagotomized dogs were mechanically respired with room air. Arterial **blood pressure** and heart rate were recorded continuously. A series of autonomic drug challenges, including angiotensin I and angiotensin II, each of which produced characteristic and reproducible **blood pressure** and

heart rate responses, was administered before and after rising intravenous doses of 0.03, 0.3, and 3.0 mg/kg of B.

1871 Compound B had no effect on **blood pressure** or heart rate at the doses tested. Compound B selectively inhibited the vasopressor response to angiotensin I while having no significant effect on angiotensin II (Table 1).

1872 TABLE 1

Effects of 2-[2-(1-carboxy-3-phenylpropyl)-amino]-1-oxopropyl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (B) on Angiotensin I and Angiotensin II Pressor Response in Anesthetized Dogs (N = 2).

Mean **Blood Pressure** Change mm. Hg  
B, mg/kg IV

	Angiotensin I	Angiotensin II
Control	51 $\pm$ 14	53 $\pm$ 15
0.03	43 $\pm$ 21	58 $\pm$ 16
0.3	8 $\pm$ 3	66 $\pm$ 14
3.0	0 $\pm$ 0	72 $\pm$ 14

sup.a Control mean **blood pressure** was 135  $\pm$  8 mm. Hg

1873 Adult mongrel dogs of either sex were anesthetized with sodium pentobarbital and ventilated artificially with a positive pressure respirator. Anesthesia was maintained by a continuous infusion of pentobarbital. Arterial **blood pressure**, left intraventricular pressure, and its first derivative dP/dt (an index of myocardial contractility), and heart rate were recorded continuously. Cardiac output, measured by thermodilution, was recorded before myocardial depression, when stable myocardial depression was achieved (approximately 30 minutes), and ten minutes following each dosage. Following surgical preparation animals were allowed 30 minutes to stabilize hemodynamically prior to induction of myocardial depression. Myocardial depression was induced and maintained by administration of dl-propranolol at 4 mg/kg IV bolus and continuous infusion of 1.125 mg/kg/min. Once stable depression was achieved, animals received either a) B at 0.3 mg/kg followed by A in rising doses from 0.01 to 1.0 mg/kg, n=6, or b) saline followed by A 0.01 to 1.0 mg/kg, n=6. Each agent was given as an IV bolus. Cardiodynamic and hemodynamic measurements were taken prior to, following stable myocardial depression, and ten minutes following each bolus injection. Ten minutes were sufficient to achieve stable response to each dose.

02/22/2000

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Page 1

11 ANSWER 3 OF 3 USPTFULL  
 AN 66:663. USPTFULL  
 TI Phenazine **ACE inhibitor** produced from streptomyces  
 species  
 IN Bush, Karen, Kingston, NJ, United States  
 Slusarchyk, Dorothy S., Belle Mead, NJ, United States  
 Liu, Wen-Chih, Princeton Junction, NJ, United States  
 1A E. R. Squibb & Sons, Inc., Princeton, NJ, United States U.S.  
 corporation  
 FI US 4568675 19860204  
 AI US 1983-562914 19831219 (6)  
 IT Utility  
 EXNAM Primary Examiner: Berch, Mark L.  
 LREP Levinson, Lawrence S.; Barrack, Donald J.  
 CLMN Number of Claims: 2  
 ECL Exemplary Claim: 1,2  
 EPWN No Drawings  
 IN.CNT 350

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Phenazine **ACE inhibitor** produced from streptomyces  
 species

FI US 4568675 19860204

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EM5523 has been analyzed and found to be 3,6-dihydroxyphenazine-1-  
 carboxylic acid, a compound having the formula ##STR1## EM5523, and  
 pharmaceutically acceptable salts thereof, are hypotensive agents. They  
 inhibit the conversion of the decapeptide angiotensin I to angiotensin  
 II and, therefore, are useful in reducing or relieving angiotensin  
 related hypertension. The action of the enzyme renin on angiotensinogen,  
 a pseudoglobulin in blood plasma, produces angiotensin I. Angiotensin I  
 is converted by angiotensin converting enzyme (ACE) to angiotensin II.  
 The latter is an active pressor substance which has been implicated as  
 the causative agent in several forms of hypertension in various  
 mammalian species, e.g., humans. EM5523 intervenes in the  
 angiotensinogen.fwdarw.(renin).fwdarw.angiotensin  
 I.fwdarw.(ACE).fwdarw.angiotensin II sequence by inhibiting angiotensin  
 converting enzyme and reducing or eliminating the formation of the  
 pressor substance angiotensin II. Thus by the administration of a  
 composition containing one (or a combination) of the compounds of this  
 invention, angiotensin dependent hypertension in a species of mammal  
 (e.g., humans) suffering therefrom is alleviated. A single dose, or  
 preferably two to four divided daily doses, provided on a basis of about  
 1.0 to 100 milligrams per kilogram of body weight per day, preferably  
 about 1 to 15 milligrams per kilogram of body weight per day, is  
 appropriate to reduce **blood pressure**. The substance  
 is administered parenterally.

11 What is claimed is:  
 2. A method of lowering **blood pressure** in a mammal  
 in need thereof, which comprises administering to said mammal an  
 effective amount of 3,6-dihydroxyphenazine-1-carboxylic acid, or a

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Page 1

pharmaceutically acceptable basic salt thereof.

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Page 1

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 FILE LAST UPDATED: 22 FEB 2000 11:12:12 PT  
 HIGHEST PATENT NUMBER: US616516  
 CA INDEXING IS CURRENT THROUGH 11 Feb 2000 11:12:12 PT  
 ISSUE CLASS FIELDS INCL CURRENT THROUGH: 11 Feb 2000 11:12:12 PT  
 REVISED CLASS FIELDS INCL LAST RECLASSIFIED: Oct 1999  
 USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Nov 1999

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 >>> the /IC5 and /IC6 fields include the corresponding catchword  
 >>> terms from the IPC subject headings and subheadings.

This file contains CAS Registry Numbers for easy and accurate  
 substance identification.

>>> ace inhibitor#:/ti,ab,clm

73 ACE/TI  
 1 ACES/TI  
 74 ACE TI  
 ((ACE OR ACES)/TI)  
 5286 INHIBITOR#/TI  
 34 (ACE INHIBITOR#)/TI  
 ((ACE(W)INHIBITOR#)/TI)  
 245 ACE/AB  
 48 ACES/AB  
 287 ACE/AB  
 ((ACE OR ACES)/AB)  
 11779 INHIBITOR#/AB  
 107 (ACE INHIBITOR#)/AB  
 ((ACE(W)INHIBITOR#)/AB)  
 376 ACE/CLM  
 141 ACES/CLM  
 496 ACE/CLM  
 ((ACE OR ACES)/CLM)  
 11616 INHIBITOR#/CLM  
 65 (ACE INHIBITOR#)/CLM  
 ((ACE(W)INHIBITOR#)/CLM)  
 11 171 (ACE INHIBITOR#)/TI,AB,CLM

=> d kwic

11 ANSWER 1 OF 171 USPATFULL

AB . . . catalytic reductive amination between ethyl  
 2-oxo-4-phenylbutyrate and alanylproline using hydrogen, a catalyst and  
 one or more additives to produce the **ACE inhibitor**,  
 enalapril.

86:11 and blood pressure

115154 BLOOD  
115159 BLOODS  
115166 BLOOD  
BLOOD OR BLOODS  
115192 PRESSURE  
115193 PRESSURES  
115194 PRESSURE  
PRESSURE OR PRESSURES  
115195 BLOOD PRESSURE  
BLOOD W PRESSURE  
12 97 11 AND BLOOD PRESSURE

86:12 KWIC 91

11 ANSWER 91 OF 97 USPATFULL

AB . . . . converting enzyme and are hypotensive agents. Hydrogenation of A58365 factors A and B, obtained by culturing Streptomyces chromofuscus, provides the **ACE inhibitors**. Also provided are C-acyl and C-sulfonyl derivatives of A and B factors which are useful in preparing deoxy factors A. . . .

SUMM The ACE inhibitory activity also can be demonstrated by the lowering of the **blood pressure** in sodium depleted rats treated with test compounds.

SUMM The ACE inhibitory compounds of the invention as described hereinabove are useful for lowering the **blood pressure** in hypertensive mammals. The compounds or the pharmaceutically acceptable non-toxic salts thereof are administered to a hypertensive host in a **blood pressure** lowering dose of between about 200 mg. and about 2,100 mg. For parenteral administration the compound or its salt or. . . .

86:12 KWIC 90-93

12 ANSWER 90 OF 97 USPATFULL

AN 86:34323 USPATFULL

TI Octahydroindolizinepropanoic acids and related compounds as enzyme inhibitors

IN Mynderse, Jon S., Indianapolis, IN, United States  
Fukuda, David S., Brownsburg, IN, United States

PA Eli Lilly Company, Indianapolis, IN, United States (U.S. corporation)

PI US 4594431 19360610

AI US 1983-519360 19830801 (6)

IT Utility

EXNAM Primary Examiner: Brust, Joseph Paul

LEP Scanlon, William B.; Whale, Arthur R.

CLM Number of Claims: 4

ECL Exemplary Claim: 1

LPWN No Drawings

ENLINT 991

AS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . . converting enzyme and are hypotensive agents. Hydrogenation of A58365 factors A and B, obtained by culturing Streptomyces chromofuscus, provides the **ACE inhibitors**. Also provided are C-acyl and C-sulfonyl derivatives of A and B factors which are useful in preparing deoxy factors A. . . .

SUMM The ACE inhibitory activity also can be demonstrated by the lowering of the **blood pressure** in sodium depleted rats treated

12 45217

with test compounds.  
 SUMMARY The ACE inhibitory compounds of the invention as described hereinabove are useful for lowering the **blood pressure** in hypertensive mammals. The compounds or the pharmaceutically acceptable non-toxic salts thereof are administered to a hypertensive host in a **blood pressure** lowering dose of between about 0.1 mg. and about 2,000 mg. For parenteral administration the compound or its salt or.

10 ANSWER 91 OF 97 USPATFULL  
 20 96:03480 USPATFULL  
 30 Method of treating heart failure and medicaments therefor  
 40 Steffen, Robert P., Saline, MI, United States  
 50 Evans, Dale B., Saline, MI, United States  
 60 Kaplan, Harvey P., Ann Arbor, MI, United States  
 70 Weissbach, Jerry A., Ann Arbor, MI, United States  
 80 Warner-Lambert Company, Morris Plains, NJ, United States U.S.  
 90 corporation

FI US 4584299 19860422  
 AI US 1984-612275 19840521 (6)  
 IT Utility  
 EXNAM Primary Examiner: Robinson, Douglas W.  
 LREP Thierstein, Joan  
 CLMN Number of Claims: 7  
 ECL Exemplary Claim: 1  
 DRWN No Drawings

LN.CNT 546  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . composition containing a combination of active ingredients including a pyridazinone or pyridin-one cardiotonic agent and a tetrahydroisoquinoline-3-carboxylic or octahydro-1H-indole-2-carboxylic acid **ACE inhibitor**.

SUMM . . . significant increase in the myocardial contractility in the pentobarbital anesthetized dog with low or minimal changes in heart rate and **blood pressure**, see U.S. Pat. No. 4,353,905 and U.S. application Ser. No. 513,799 of July 12, 1983.

DETL Barbiturate anesthetized, vagotomized dogs were mechanically respired with room air. Arterial **blood pressure** and heart rate were recorded continuously. A series of autonomic drug challenges including angiotensin I and angiotensin II, each of which produced characteristic and reproducible **blood pressure** and heart rate responses, was administered before and after rising intravenous doses of 0.03, 0.3, and 3.0 mg/kg of B.  
 DETD Compound B had no effect on **blood pressure** or heart rate at the doses tested. Compound B selectively inhibited the vasopressor response to angiotensin I while having no.

DETE TABLE 1

Effects of 2-[2-[(1-carboxy-3-phenylpropyl)-amino]-1-oxopropyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (B) on Angiotensin I and Angiotensin II Pressor Response in Anesthetized Dogs (N = 2)

Mean **Blood Pressure** Change (mm Hg)  
 B, mg/kg IV  
 Angiotensin I  
 Angiotensin II

Control sup.a		
	51 .+- . 14	52 .+- . 15
0.03	43 .+- . 21	50 .+- . 16
0.3	8 .+- . 3	66 .+- . 14
3.0	0 .+- . 0	72 .+- . 14

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... Control mean **blood pressure** was 115 mm Hg.  
... sodium pentobarbital and ventilated artificially with a  
positive pressure respirator. Anesthesia was maintained by a continuous  
infusion of pentobarbital. Arterial **blood pressure**,  
left intraventricular pressure, and its first derivative at an index  
of myocardial contractility, and heart rate were recorded continuously  
cardiac.

12 ANSWER 92 OF 97 USPATFULL  
AN 86:0630 USPATFULL  
TI Phenazine **ACE inhibitor** produced from streptomyces  
species  
IN Bush, Karen, Kingston, NJ, United States  
Slusarskyk, Dorothy S., Belle Mead, NJ, United States  
Liu, Wen-Chih, Princeton Junction, NJ, United States  
PA E. R. Squibb & Sons, Inc., Princeton, NJ, United States U.S.  
corporation  
FI US 4568675 19860204  
AI US 1983-562914 19831219 46  
IT Utility  
EXNAM Primary Examiner: Berch, Mark L.  
LREP Levinson, Lawrence S.; Barrack, Ronald C.  
CLMN Number of Claims: 2  
ECL Exemplary Claim: 1,2  
IRWN No Drawings  
LN.CNT 350

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Phenazine **ACE inhibitor** produced from streptomyces  
species

SUMM . . . . weight per day, preferably about 1 to 15 milligrams per  
kilogram of body weight per day, is appropriate to reduce **blood**  
**pressure**. The substance is administered parenterally.

CLM What is claimed is:

2. A method of lowering **blood pressure** in a mammal  
in need thereof, which comprises administering to said mammal an  
effective amount of 3,6-dihydroxyphenazine-1-carboxylic acid, or a . . .

12 ANSWER 93 OF 97 USPATFULL  
AN 85:72392 USPATFULL  
TI Cardiovascular composition  
IN Chan, Chi-Chung, Kirkland, Canada  
Ford-Hutchinson, Anthony W., Beaconsfield, Canada  
PA Merck & Co., Inc., Rahway, NJ, United States U.S. corporation  
FI US 4558037 19851210  
AI US 1984-617293 19840604 (6)  
IT Utility  
EXNAM Primary Examiner: Phillips, Delbert R.  
LREP Mitri, Salvatore C.; Sudol, Michael C.  
CLMN Number of Claims: 12  
ECL Exemplary Claim: 1  
IRWN No Drawings  
LN.CNT 386

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . . cardiovascular composition is disclosed which comprises either  
dibenzo-thiepin derivatives alone or the combination of dibenzo-thiepin  
derivatives and angiotensin converting enzyme **ACE**  
**inhibitors**. These compositions represent a novel therapeutic  
approach to thromboembolic disease in man.  
DETX . . . . 15 minutes later by the second stimulation. Hexamethonium and  
hydralazine were co-administered in order to induce a drop in systemic  
**blood pressure** without a reflex increase in heart

rate.  
HITD Because it has been reported that Enalapril lowers **blood pressure** in several animal models of experimental hypertension (C. S. Sweet et al., Fed. Proc., 41, 167-171, 1982 and C. S. Sweet et al., J. Pharmacol., 76, 167-176, 1981), it was necessary to examine in separate experiments whether Enalapril and HITD produced effects upon **blood pressure** and heart rate in this model. In particular, it was important to determine whether the cardiovascular effects of the HITD-Enalapril combination for the observed changes in platelet accumulation. As shown in Table II below, a combination of HITD and Enalapril decreased **blood pressure** a reduction of  $14.4 \pm 1.3$  mm Hg and heart rate substantially in anesthetized rabbits. The hypotensive effect was mainly attributable to Enalapril because HITD by itself had no significant cardiovascular actions. **blood pressure** before and after treatment with HITD was  $41.4 \pm 1.6$  mm Hg and  $39.4 \pm 1.3$  mm Hg, respectively,  $n=6$ . In the group treated with Enalapril only, **blood pressure** before and after treatment was  $54.4 \pm 1.7$  mm Hg and  $29.4 \pm 1.4$  mm Hg, respectively,  $n=8$ , a decrease of  $25.4 \pm 1.9$  mm Hg. A combination of hexamethonium and hydralazine, which act by a different mechanism than Enalapril, i.e., by non-specific vasodilation, also lowered **blood pressure** to a similar extent to that observed for HITD and Enalapril (Table II). However, there is no evidence for synergism.